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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,949	OMARY ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *5 and 8-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/17/05, 1/24/07, 3/14/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply with Sequence Rules*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, drawn to methods for detecting a genotype of K8 by analyzing nucleic acids, and the particular mutation of K8 R340X in the replies filed on April 21, 2008 and May 29, 2008 is acknowledged. The traversal is on the ground(s) that there would not be any undue burden to examine methods for determining a genotype of the nucleic acid K8 together with methods for determining the genotype of the nucleic acid of K18. Applicants assert that these nucleic acids encode for proteins that are obligate heterodimers. This argument has been fully considered but is not found persuasive because it is maintained that undue burden would be required to examine methods for determining the genotype of K8 together with methods for determining the genotype of K18. The nucleic acid encoding K8 consists of a distinct nucleotide sequence as compared to the nucleic acid encoding K18 and K8 and K18 include distinct mutations. Thereby, a sequence search and keyword search of methods for determining a genotype of K8 would not be co-extensive with a sequence search and keyword search of methods for determining. Applicants further assert that Groups I and III should be considered together and Groups II and IV should be considered together because one can analyze for mutations in proteins and this is an alternative method of detecting keratin mutations. These arguments are not convincing methods of detecting mutations in a nucleic acid require the use of different method steps and reagents as compared to methods for detecting mutations in proteins. Additionally, a search for methods for detecting mutations in nucleic acids is distinct from a search for

methods for detecting mutations in proteins. Further, the restriction requirement is proper because no special technical feature links the distinct inventions since the linking feature of keratin K8 was known in the art at the time the invention was made (see page 3 of the Restriction Requirement of March 19, 2008).

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-4, 6 and 7 have been examined herein only to the extent that the claims read on the elected methods which detect a genotype of K8 by assaying nucleic acids. Further, claims 3 and 4 have been examined only to the extent that the claims read on the K8 R340X mutation.

Claim Objections

3. Claims 1-4, 6, and 7 are objected to because the claim includes subject matter of the non-elected inventions, namely the detection of a mutation in a protein (Groups III and IV), the detection of a phenotype (Group V and VI), the detection of K18 (Groups II, IV and VI), and with respect to claims 3-4, 6 and 7, the detection of the mutations other than K8 R340X.

Specification

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821-25 because the previously submitted Sequence Listing does not include each of the sequences set forth in the present application. See, for example, Figures 1B and 3A and page 2 of the specification. In response to this Office action, Applicants must

comply with the requirements of 37 CFR 1.821-1.825. In particular, Applicant is required to submit a CRF and paper copy of the Sequence Listing containing the recited sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the specification for the brief description of the drawings and/or submitting a new drawing for Figure 1 and Figure 3 including the appropriate SEQ ID NOs, and a letter stating that the content of the paper and computer readable copies are the same.

5. The disclosure is objected to because of the following informalities:

The specification (pages 5 and 6) refers to the sequences of SEQ ID NO: 1-4. However, the specification does not include a sequence listing, and particularly does not include a sequence listing that provides the sequences of SEQ ID NO: 1-4.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 6 and 7 are indefinite because the claims do not recite a clear nexus between the preamble of the claims and the final process step of the claims. The claims are drawn to methods for detecting a predisposition to liver disease. However, the claims recite a final step of analyzing an individual for a quantitative or qualitative

change in a genotype of Keratin K8. The claims do not set forth how analysis of an individual for a quantitative or qualitative change in a genotype results in the detection of a predisposition to a liver disease. Accordingly, it is unclear as to whether the claims are intended to be limited to methods for determining a predisposition to liver disease or methods for detecting a quantitative or qualitative change in a genotype of keratin K8.

Claims 1-4, 6 and 7 are indefinite over the recitation of a quantitative or qualitative change in a genotype of keratin K8. This phrase is not clearly defined in the specification and there is no art recognized definition for this phrase. Accordingly, one of skill in the art cannot determine the meets and bounds of the claimed subject matter.

Claims 3, 4, 6 and 7 are indefinite over the recitation of “said human keratin” because this phrase lacks proper antecedent basis. It is also unclear as to how this phrase is intended to limit the claims. The claims recite the phrase that "said keratin is one or more of K8 G52X...". However, the recited list includes mutations in the keratin protein and not “human keratin” per se. Additionally, the claims do not set forth a relationship between the genotype of keratin K8 and the human keratin of K8 R340X.

Claims 3, 4, 6 and 7 are indefinite over the recitation of “the naturally occurring amino acid” because this phrase is not defined in the specification or claims and it is unclear as to what constitutes a naturally occurring amino acid with respect to the stated mutations. For example, it is unclear as to whether the “naturally occurring amino acid” is any of the standard 20 naturally occurring amino acids, or is limited to only the amino acid of arginine or is limited to the known amino acid variations at position 304 of an arginine or histidine.

Claims 6 and 7 are indefinite over the recitation of "said analyzing the genomic or mRNA sequences" because this phrase lacks proper antecedent basis since the claims do not previously recite a step of analyzing genomic or mRNA sequences.

Claim Rejections - 35 USC § 112 – Written Description

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

In analyzing the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note that with regard to genus/species situations, a "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

To ascertain whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been

described by their complete structure. It is then determined whether a representative number of species have been defined by other identifying characteristics.

In the present situation, the claims are drawn to methods for detecting a predisposition to any type of liver disease (claim 1) or any type of noncryptogenic liver disease (claim 2) in an individual wherein the method comprises detecting a quantitative or qualitative change in a genotype of keratin K8. The claims thereby encompass detecting any genotype of a keratin K8 gene. The claims do not define the genotype in terms of any particular structural features, such as the location of a mutation (i.e., nucleotide position or amino acid position), the identity of the mutation (A, G, C or T) or the type of mutation (e.g., insertion, deletion, substitution of one or more nucleotides). Further, claims 1 and 2 encompass detecting the mutation in any "individual," and thereby include detecting a keratin 8 mutation in any non-human animal, including dogs, goats, horses, monkeys, rats etc.

The claimed genus of genotypes (mutations) is considered to be potentially significantly large. The keratin 8 gene is 7,890 nucleotides in length and 80 mutations are currently known to be present in this gene in humans (see Gene Card for keratin 8 available via url: <genecards.org/cgi-bin/carddisp.pl?gene=krt8>). At least 9 orthologs of this gene are known to exist in dogs, chimpanzees, rat, mice, chicken, zebrafish, African clawed frog, tropical clawed frog and rainbow trout.

However, the specification (Table 3) discloses only 14 mutations in the human keratin 8 gene encoding for the mutations: G52V, Y53H, G61C, R340H, G433S, R453C, I-465(I) RDT (468), I62V, L71L (CTG to CTA), A318S, R201C (CGC to TGC),

E376E (GAG to GAA), V460M and V479I. The I62V, A318S, R201C (CGC to TGC), V460M and V479I are described as polymorphisms that are found at similar or higher incidence in controls as compared with individuals having liver disease (see footnote to Table 3). Accordingly, the specification describes in terms of its complete structure 9 mutations in the human keratin 8 gene that are asserted to be associated with the occurrence of liver disease.

Thereby, while the specification has adequately described the human keratin 8 mutations of G52V, Y53H, G61C, R340H, G433S, R453C, I-465(I) RDT (468), L71L (CTG to CTA), and E376E (GAG to GAA), the specification has not adequately described any additional keratin K8 mutations in humans or any keratin K8 mutations in non-human individuals, wherein the genotype comprising the mutation is associated with liver disease and particularly with noncryptogenic liver disease.

Further, no additional members of the claimed genus have been sufficiently described in terms of any other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein product, etc.).

Additionally, the specification does not disclose a clear structure-function relationship between the claimed mutation and their association with liver disease. There is no showing or evidence which links particular nucleotides in the keratin 8 gene with particular functional properties correlated with liver disease. The specification (page 27) discusses the potential effects of 4 of the mutations. Namely, the specification suggests that the R340H mutation may be correlated with destabilization, the G433S mutation may be associated with altering keratin phosphorylation, the R453 mutation

may be correlated with formation of a disulfide bond and the 1-465(I) RDT (468) mutation may be associated with destablilization. However, the specification does not teach any additional critical sequences or domains in keratin 8 that are required to impart the function of causing or otherwise being associated with any type of cryptogenic or noncryptogenic form of liver disease. In the absence of any real structure-function relationship and in the absence of a representative number of species of the claimed genus, there is insufficient descriptive support for the currently claimed genus of any genotype of a human or non-human keratin 8 gene.

The decisional law in this area has been very consistent. The Federal Circuit in Lilly, Fiers, Rochester and many other cases has determined that the written description issue applies to situations where the definition of the subject matter of the claims fails to provide description commensurate with the genus. The most recent case law directly supports this rejection. As the District Court in University of Rochester v. G.D. Searle & Co., Inc. (2003 WL 759719 W.D.N.Y.,2003. March 5, 2003.) noted "In effect, then, the '850 patent claims a method that cannot be practiced until one discovers a compound that was not in the possession of, or known to, the inventors themselves. Putting the claimed method into practice awaited someone actually discovering a necessary component of the invention." This is similar to the current situation since the breadth of the current claims comprises the detection of any genotype in the keratin 8 gene which the present inventors were not in the possession of, or which were not known to the inventors. In a genus that is possibly quite immense, the specification discloses only methods which 9 particular mutations in the human keratin k8 gene as indicative of

particular types of liver disease - i.e., the mutations encoding for a G52V, Y53H, G61C, R340H, G433S, R453C, I-465(I) RDT (468), L71L (CTG to CTA), and E376E (GAG to GAA) mutation.

As noted in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), the Federal Circuit concluded that:

"...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

With respect to the present invention, there is no record or description which would demonstrate conception of any mutations or variations in the keratin 8 gene of nonhuman animals or any mutations or variations in the keratin 8 gene of humans other than the mutations encoding G52V, Y53H, G61C, R340H, G433S, R453C, I-465(I) RDT (468), L71L (CTG to CTA), and E376E (GAG to GAA) . Therefore, the claims fail to meet the written description requirement because the claims encompass a significantly large genus of polynucleotide sequences which are not described in the specification.

Claim Rejections - 35 USC § 112 - Enablement

8. Claims 1-4, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying a human subject at increased risk for viral hepatitis or acute fulminant hepatitis (AFH) comprising: (a) providing a nucleic acid sample from said human subject wherein the nucleic acid sample comprises a nucleic acid encoding keratin 8; (b) analyzing the sequence of the

nucleic acid encoding keratin 8 to determine the identity of the nucleotides encoding codon 340; and (c) determining that said human subject has an increased risk for viral hepatitis or AFH if said human subject has the sequence CAT at codon 340 of the nucleic acid encoding keratin 8 as compared to a human subject that has the sequence CGT at codon 340 of the nucleic acid encoding keratin 8, does not reasonably provide enablement for methods for determining a predisposition to any cryptogenic or noncryptogenic liver disease in any human or nonhuman subject by determining any qualitative or quantitative change in any genotype of the keratin k8 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 1 and 2 are drawn to methods for detecting a predisposition to any type of liver disease (claim 1) or any type of noncryptogenic liver disease (claim 2) in an individual wherein the method comprises detecting a quantitative or qualitative change in a genotype of keratin K8. The claims thereby encompass detecting any genotype of a

keratin K8 gene. The claims do not define the genotype in terms of any particular structural features, such as the location of a mutation (i.e., nucleotide position or amino acid position), the identity of the mutation (A, G, C or T) or the type of mutation (e.g., insertion, deletion, substitution of one or more nucleotides). Further, claims 1 and 2 encompass detecting the mutation in any "individual," and thereby include detecting a keratin 8 mutation in any non-human animal, including dogs, goats, horses, monkeys, rats etc. Thereby, the claims encompass the detection of a potentially large genus of genotypes that have not been clearly described in terms of any particular structural features.

Claims 3, 6 and 7 recite that the “human keratin is… K8 R340X…, where X is any amino acid other than the naturally occurring amino acid or a deleted amino acid.” In view of the "human keratin" language, the claims have been interpreted as being limited to methods which detect the genotype of the keratin K8 gene in a human subject. However, as broadly written, the claims encompass detecting a nucleotide alteration resulting in any amino acid change at position 340 of keratin 8 or resulting in a deletion of the amino acid at position 340 of keratin 8. Claim 4 is considered to be limited to methods wherein the mutation is in the human keratin 8 gene and encodes for the R340H mutation.

Claim 1 encompasses the detection of a predisposition to any liver disease and claims 2-4, 6 and 7 encompass the detection of a predisposition to any noncryptogenic liver disease. Thus the claims encompass the diagnosis of a predisposition to a wide variety of liver diseases including liver diseases associated with viral hepatitis, alcohol,

cystic fibrosis, tumors, polycystic disease, parenteral nutrition-induced, multiple adenomas, and congenital hepatic fibrosis. (see, e.g., Table 2 of the specification).

Further, the claims recite the language of "analyzing an individual for quantitative or qualitative change" in a genotype. This language is not clearly defined in the specification or claims and the claims do not recite any particular limitations as to how a quantitative or qualitative change is determined in a genotype. Accordingly, the claims appear to encompass methods wherein a change in a genotype is detected as a change in the quantity of keratin 8 mRNA or DNA, or a change in a genotype from heterozygous to homozygous.

Nature of the Invention

The claims are drawn to methods for detecting a predisposition to a liver disease by assaying for a genotype of a keratin 8 gene. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification (page 5) teaches that the keratin 8 nucleic acid sequence was known in the art at the time the invention was made and is provided in GenBank Accession No. NM_002273. The specification further teaches that the keratin 8 nucleic acid sequence is provided as SEQ ID NO: 3 and the amino acid sequence is provided as SEQ ID NO: 4 therein.

The specification teaches the results of a study in which 467 liver explants from patients having liver disease and 349 healthy control blood samples were analyzed for the presence of mutations in the K8 gene. Based on this analysis, the specification identified 14 mutations that were present in the K8 gene – i.e., the mutations encoding for mutations: G52V, Y53H, G61C, R340H, G433S, R453C, I-465(I) RDT (468), I62V, L71L (CTG to CTA), A318S, R201C (CGC to TGC), E376E (GAG to GAA), V460M and V479I (see Table 3). The I62V, A318S, R201C (CGC to TGC), V460M and V479I are described as polymorphisms that are found at similar or higher incidence in controls as compared with individuals having liver disease (see footnote to Table 3). Nine of the mutations are characterized as posing "a potential risk factor for subsequent development of liver cancer" (see footnote for Table 3). However, 3 of these mutations, namely the G52V, R453C and I-465(I) RDT(468) mutations, were found in only a single patient (i.e., 1 out of 467 patients) having liver disease. While the 3 mutations were not found in any of the 349 control blood samples, no results are provided for control liver samples. Given the fact that the 3 mutations were found in only a single patient and that the sample control population was not of an equivalent size as compared to the affected patient population and that no control liver samples were analyzed, the results obtained from this analysis would not be accepted by those of skill in the art as providing a conclusive correlation between the presence of the mutations and liver disease.

With respect to the elected mutation, the specification teaches that the C<u>G</u>T to C<u>A</u>T mutation encoding for an Arg to His substitution at codon 340 was present in 30/467 (6.4%) human subjects having liver disease and in 10/349 (2.9%) control human

subjects (Table 3). The specification further teaches that the K8 R340H mutation was found in human patients having viral hepatitis and in patients with acute fulminant hepatitis (AFH; Table 4). Accordingly, the description has enabled methods of determining whether a human patient has a predisposition to viral hepatitis or AFH by detecting the K8 R340H mutation. However, the specification has not enabled methods for detecting the R340H mutation as indicative of any other liver disease in human or nonhuman subjects. Further, the specification has not enabled detecting a predisposition to a liver disease by detecting a change in any qualitative or quantitative trait of any keratin 8 nucleic acid, such as a change in the quantity of keratin 8 mRNA or DNA.

The Predictability or Unpredictability of the Art :

The art of identifying polymorphisms and determining their association with a disorder, such as liver disease, is highly unpredictable. Knowledge of the sequence of the wildtype keratin 8 gene does not allow one to predict the identity of mutations/polymorphisms in the keratin 8 gene which are correlated with the occurrence of any particular type or all types of liver disease. Polymorphisms are known to occur at a frequency of approximately 1 out of every 1000 bases in the human genome. However, there is no predictable means for distinguishing between polymorphisms which will be correlated with liver disease and polymorphisms which will not be correlated with the liver disease.

The teachings in the specification support the unpredictability of establishing a correlation between a mutation/polymorphism and the occurrence of liver disease. In

particular, the specification (table 3) teaches that while the I62V, A318S, R201C (CGC to TGC), V460M and V479I mutations were present in subjects having liver disease, these mutations were present at a similar or higher incidence in control subjects that do not have liver disease.

Moreover, it is well recognized in the art that the associations between polymorphisms and phenotypic traits are often irreproducible. For example, Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

It is also highly unpredictable as to whether the results obtained in the present study can be extrapolated to other ethnic groups. This finding is supported by the teachings of Halushka (Nature. July 1999. 22: 239-247). Halushka studied the frequency of polymorphisms among different ethnic populations and between human and apes. The reference (see abstract, page 244 col. 2 and page 245, col 1) found that

there was considerable diversity in the number and frequency of SNPs between different ethnic groups and between humans and orthologous great ape sequences.

The post-filing date art supports the unpredictability of detecting mutations in the keratin 8 gene as diagnostic of a predisposition to liver disease. For example, Hesse (Journal of Medical Genetics. 2004. 41: e42) analyzed the keratin 8 gene in 256 European Caucasians having diverse liver diseases, but did not detect any amino acid altering mutations in these subjects. A g.740A>G variation was detected in both patients with liver disease and in control subjects. A g.418-4C>G mutation in intron 1 was also detected, but only in one patient with HBV (see page 2, col. 2). Hesse concluded that "(t)he contrary result of our study to the mutations reported so far suggests that allele frequencies might possibly differ between European and North American populations. It might be also possible that additional risk factors coincide with K8 and K18 mutations in Northern American but not European liver patients" (page 3, col. 1).

Similarly, Halangk et al (Journal of Medical Genetics. 2004. 41: e92) studied the prevalence of Y54H and G62C keratin 8 mutations in a population of 1668 patients with liver disease and 679 healthy controls. Halangk did not find an association between the occurrence of these mutations and cryptogenic or noncryptogenic liver disease (page 2, col. 2). The authors indicated that one reason for the discrepancy in the results with those of prior studies may be the fact that their study analyzed subjects having a greater ethnic homogeneity (page 2, final para to page 3, first para).

Additionally, the present claims encompass methods which determine a predisposition to any liver disease by assaying for a R340H mutation. However, the

data provided in the specification is limited to the detection of the R340H mutation in subjects having viral hepatitis or AFH. The specification does not teach the frequency of occurrence of the R340H mutation in other types of liver disease, such as cystic fibrosis or liver tumors. It is highly unpredictable as to whether the results obtained with one type of liver disease can be extrapolated to other types of liver disease.

The teachings in the prior art support the unpredictability of extrapolating the findings of an association between a keratin 8 mutation and one type of liver disease to all other types of liver disease. In particular, by Ku et al (The New England Journal of Medicine, May 2001. 344: 1580-1587; cited in the IDS of November 17, 2005) detected the Gly61Cys and Tyr53His mutations in subjects having cryptogenic cirrhosis, but did not detect these mutations "in the patients with other liver diseases" (see abstract). The "other liver diseases" in which the mutations were not present include hepatitis C, autoimmune hepatitis, acute fulminant hepatitis, primary bilary cirrhosis, Wilson's disease, hepatitis B and neonatal hepatitis (page 1581, para 1).

Further, claims 1 and 2 encompass determining a predisposition to liver disease in any individual. The specification does not define the term "individual" and thereby the claims include determining a predisposition to liver disease in any non-human animal, such as in a goat, rat, dog, horse, chimpanzee etc. However, the specification does not teach the occurrence of keratin 8 mutations, and particularly the R340H mutation, in a representative number of distinct animals, and an association between keratin 8 mutations or the R340H mutation and various liver diseases. The specification does not disclose a clear structure-function relationship between the claimed mutation and their

association with liver disease. There is no showing or evidence which links particular nucleotides in the keratin 8 gene with particular functional properties correlated with liver disease. The specification (page 27) discusses the potential effects of 4 of the mutations. Namely, the specification suggests that the R340H mutation may be correlated with destabilization, the G433S mutation may be associated with altering keratin phosphorylation, the R453 mutation may be correlated with formation of a disulfide bond and the 1-465(I) RDT (468) mutation may be associated with destablilization. However, the specification does not teach any additional critical sequences or domains in keratin 8 that are required to impart the function of causing or otherwise being associated with any type of cryptogenic or noncryptogenic form of liver disease. The specification (page 28) also teaches that while there are a number of potential functions associated with keratin that may effect liver disease, "the mechanisms by which keratin mutations predispose to cirrhosis remain to be defined." Accordingly, in the absence of a clear structure-function relationship between keratin 8 mutations and the occurrence of liver disease, and in the absence of a representative number of keratin 8 mutations in diverse animals, it is unpredictable if the presence of a qualitative or quantitative change in a keratin 8 genotype can be detected as indicative of liver disease.

The present claims also include determining a quantitative or qualitative change in a keratin 8 genotype. Accordingly, the claims include detecting a change in the quantity of keratin 8 mRNA or DNA. However, it is unpredictable as to whether a change in keratin 8 mRNA levels or chromosomal or extrachromosomal levels occur in

subjects having keratin 8 mutations, and whether such changes are correlated with the occurrence of any or all liver diseases.

Amount of Direction or Guidance Provided by the Specification and Degree of Experimentation:

The specification does not provide sufficient guidance as to how to detect additional polymorphisms in the keratin 8 gene as indicative of any type of cryptogenic or noncryptogenic liver disease. Extensive experimentation would be required to identify additional genotypes associated with cryptogenic or noncryptogenic liver disease. For example, such experimentation may involve sequencing the keratin 8 gene of individuals having cystic fibrosis to identify mutations, sequencing the keratin 8 gene of individuals that do not have cystic fibrosis, determining the frequency of any mutation present in the individuals having cystic fibrosis and not present in individuals that do not have cystic fibrosis, and performing a statistical analysis to determine whether there is a statistically significant increase or decrease in the occurrence of a mutation in individuals having cystic fibrosis as compared to individuals that have not had cystic fibrosis. Further experimentation may also include performing the above method in a representative number of human subjects having and not having other forms of liver disease, such as hepatitis C, cirrhosis, neonatal hepatitis, liver cancer etc. Additionally, the experimentation may include performing the above methods in a representative number of diverse ethnic populations and in a representative number of distinct animals. Because the outcome of such experimentation cannot be predicted, such experimentation is considered to be undue.

While methods for sequencing nucleic acids are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for polymorphisms that may linked to a particular phenotype. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional mutations in the keratin 8 gene associated with a representative number of diverse types of liver disease.

Working Examples:

The specification provides a working example in which human subjects having viral hepatitis or AFH were genotyped for a mutation in the sequence of the keratin 8 gene encoding codon 340, and the presence of a mutation encoding for a histidine at codon 340 was detected.

However, no working examples are provided wherein the presence of any other alteration at codon 340, including any other amino acid substitution or a deletion of amino acid 340 was detected as indicative of liver disease.

No working examples are provided wherein the R340H mutation is detected as indicative of other types of liver disease, such as neonatal hepatitis or liver cancer.

No working examples are provided wherein other qualitative or quantitative changes in a keratin 8 genotype, such as a change in mRNA or DNA levels or a change from homozygous to heterozygous, is detected as indicative of any liver disease.

No working examples are provided wherein any non-human animal subject is determined to have a liver disease by analyzing a qualitative or quantitative change in a

genotype of keratin 8, or by specifically detecting the presence of a R340X mutation in keratin 8.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches an association only between the R340H keratin 8 mutation and the occurrence of viral hepatitis or AFH in human subjects, whereas the claims encompass methods for detecting any qualitative or quantitative change in any keratin 8 genotype as indicative of any type of cryptogenic or noncryptogenic liver disease in a human or non-human subject. The specification does not teach a representative number of keratin 8 mutations that can be used to identify an individual predisposed to any type of liver disease. The specification also does not

teach that non-human subjects can be determined to have a predisposition to liver disease by detecting a keratin 8 genotype. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Ku et al (Molecular Biology of the Cell. Nov 2001. 12, Supplement 1, page 56a, abstract #303; cited in the IDS of November 17, 2005). Ku teaches methods for detecting the presence of mutations in the keratin 8 gene. In particular, Ku analyzed the keratin 8 gene of 323 patients having noncryptogenic liver disease and 200 normal control individuals for the presence of mutations. Ku detected the presence of the Y53H and G61C mutation in a variety of liver diseases, including biliary atresia, hepatitis B and C, alcohol, primary biliary cirrhosis, neonatal hepatitis, congenital hepatic fibrosis, and acute fulminant hepatitis. Ku concluded that K8 mutations “are associated with variety of liver diseases and pose a risk factor for the subsequent development of liver disease.” Accordingly, Ku is considered to teach a method comprising the step of

analyzing an individual for a qualitative change in the genotype of keratin 8 – i.e., detecting a mutation in the keratin 8 gene.

10. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Ku et al (The New England Journal of Medicine, May 2001. 344: 1580-1587; cited in the IDS of November 17, 2005).

Ku et al teaches methods for detecting the presence of mutations in the keratin 8 gene. In particular, Ku analyzed the keratin 8 gene of patients having liver disease and normal control individuals for the presence of mutations. Ku detected the presence of the Y53H and G61C mutations in the keratin 8 gene of patients having cryptogenic liver disease. These mutations were not found in patients with other types of liver disease or in control patients. Ku concluded that the Y53H and G61C mutations are associated with the occurrence of cryptogenic liver disease. Accordingly, Ku is considered to teach a method comprising the step of analyzing an individual for a qualitative change in the genotype of keratin 8 – i.e., detecting a mutation in the keratin 8 gene.

11. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Ku et al (Gastroenterology. published 26 March 2002. Vol. 122, Supplement 4, p A80, abstract #665; cited in the IDS of November 17, 2005).

Ku et al teaches methods for detecting the presence of mutations in the keratin 8 gene. In particular, Ku analyzed the keratin 8 gene of patients having liver disease and normal control individuals for the presence of mutations. Ku detected the presence of the Y53H mutation in the keratin 8 gene of patients having cryptogenic

liver disease, viral hepatitis, and biliary atresia, and the G61C mutation in patients having cryptogenic liver disease, viral hepatitis, cystic fibrosis. Additionally, a K8 G52V mutation was detected in one patient having viral hepatitis. Ku discloses that each of these mutations are associated with the occurrence of cryptogenic and noncryptogenic liver disease. Accordingly, Ku is considered to teach a method comprising the step of analyzing an individual for a qualitative change in the genotype of keratin 8 – i.e., detecting a mutation in the keratin 8 gene.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/
Primary Examiner, Art Unit 1634